UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/574,386	05/19/00	ALBERTSON D	M-9144 US

022798
LAW OFFICES OF JONATHAN ALAN QUINE
P O BOX 458
ALAMEDA CA 94501

HM12/0920

EXAMINER	
SPIEGLER, A	

ART UNIT	PAPER NUMBER
1656	10

DATE MAILED: 09/20/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/574,386	ALBERTSON ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1656	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. This action is in response to Paper No. 9, filed on June 22nd, 2001. Currently, claims 1-22 are pending. All arguments have been full considered and thoroughly reviewed, but are deemed not persuasive for the reasons which follow. This action is made FINAL. Any objections and rejections not reiterated below are hereby withdrawn.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-22 are indefinite over the recitation of "the corresponding first polynucleotide" because this recitation lacks antecedent basis.

B) Claims 1-22 are indefinite over the recitation of "the corresponding first polynucleotide" because it is not clear as to what "the corresponding first polynucleotide" is. Furthermore, it is not clear as to how a target solution is representative of the corresponding first polynucleotide. (i.e. it is not clear as to how one determines whether or not a target solution is representative of the corresponding first polynucleotide).

MAINTAINED REJECTIONS

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 3-13, and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS).

Smith teaches ligation-mediated PCR of restriction fragments from large DNA molecules. The reference teaches a method of PCR that involves sequence-specific ligation of "adapter-tags", which provide a target for primer annealing subsequent PCR reactions (abstract). Another adapter (i.e. "bubble-tags") provide a second target for primer annealing (abstract). Smith teaches that the advantage of this method is that specific fragments can be isolated without any prior knowledge of the nucleotide sequence of the target (abstract). Furthermore, the reference teaches that the method provides a means to amplify fragments of any DNA molecule ranging from about 50 to 25 kb in size (pg. 21). The reference also teaches that the "adapter-tags" contain a second strand having a region of substantial complementarity to a region of the first strand (pg. 21-22, Table 1). The reference also teaches that the amplification product can be isolated (pg. 24), and can then be resuspended to form a target solution. The claims recite "preparing amplification products useful for forming an array" and "resuspending each amplification product to form a target solution suitable for application to a substrate". The claims do not specifically require performing an active process step of applying the amplification products to a substrate. Also, it is a property of Smith's target solution comprising amplification

products, that this target solution would be suitable for application to a substrate. Smith also teaches that the ligase-mediated PCR technique can be used from polynucleotides derived from large molecules, such as YAC (pg. 25). With respect to claim 10, the reference teaches the use of a type IIS restriction endonucleases (abstract). With respect to claims 11-13, the reference teaches that sequence runs of 350 basepairs were used.

Applicants' traverse the anticipation rejection of Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS). Applicants' argue that "The Examiner's rationale does not take into account the fact that the method of claim 1 produces a plurality of target solutions, each of which is "***representative of the corresponding first polynucleotide***". Applicants further argue that Smith teaches "a general method...for PCR amplification of single restriction fragments (emphasis added) from large DNA molecules", whereas applicants teach representative target solutions conveniently produced by fragmenting a starting polynucleotide (pg. 4 of response), and seeks to produce an amplification product that is representative of the "entire" starting polynucleotide, not just a fragment (pg. 5 of response). Applicants also argue that a multiplex variation of the Smith method would not be practicable for producing an amplification product that is representative of the corresponding starting polynucleotide.

Applicants' argue that "The Examiner's rationale does not take into account the fact that the method of claim 1 produces a plurality of target solutions, each of which is "***representative of the corresponding first polynucleotide***". This argument is not persuasive because Smith (pg. 22, Fig. 1) teaches the production of a plurality of target solutions, which are all derived from the same target DNA (i.e. representative of "the corresponding first polynucleotide"). The PCR products (shown in Figure 1), would contain DNA from the original target DNA (i.e. the first

polynucleotide), and therefore, the plurality of PCR products would be representative of the starting polynucleotide.

Applicants further argue that Smith teaches "a general method...for PCR amplification of single restriction fragments (emphasis added) from large DNA molecules", whereas applicants teach representative target solutions conveniently produced by fragmenting a starting polynucleotide (pg. 4 of response), and seeks to produce an amplification product that is representative of the "entire" starting polynucleotide, not just a fragment (pg. 5 of response). This argument is not persuasive for several reasons. First, Applicants have not demonstrated a clear difference between the method of Smith and the method of the present invention. Smith teaches the production of target solutions produced by fragmenting a starting polynucleotide (Figure 1). Applicants state "as described in the specification, representative target solutions conveniently produced by fragmenting a starting polynucleotide (pg. 4 of response)". Therefore, the method of Smith clearly anticipates the method of the present invention. In addition, applicants argue that the amplification products of the present invention are representative of the "entire" starting polynucleotide, not just a fragment (pg. 5 of response). This argument is not persuasive, as Applicants' are arguing limitations not found in the claims. The claims only require that the target solution is "representative of the corresponding first polynucleotide", and therefore, the claims do not specify that the target solutions must be representative of the "entire" starting polynucleotide, not just a fragment.

Applicants also argue that a multiplex variation of the Smith method would not be practicable for producing an amplification product that is representative of the corresponding starting polynucleotide. This argument is not persuasive because Smith (pg. 26, col. 2) teaches

that other possible applications of his method include fingerprinting purified cosmids, YACs ,or even bacterial genomes, and multiplex chromosome walking in clone libraries arrayed in high density grids. Therefore, a multiplex variation of the Smith method would be practicable for producing an amplification product that is representative of the corresponding starting polynucleotide.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 2, 14-16 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), in view of Brown et al. (US 5,807,522, cited in the IDS).

Smith teaches ligation-mediated PCR of restriction fragments from large DNA molecules. The reference teaches a method of PCR that involves sequence-specific ligation of "adapter-tags", which provide a target for primer annealing subsequent PCR reactions (abstract). Another adapter (i.e. "bubble-tags") provide a second target for primer annealing (abstract). Smith teaches that the advantage of this method is that specific fragments can be isolated without any prior knowledge of the nucleotide sequence of the target (abstract). Furthermore, the reference teaches that the method provides a means to amplify fragments of any DNA molecule ranging from about 50 to 25 kb in size (pg. 21). The reference also teaches that the "adapter-tags" contain a second strand having a region of substantial complementarity to a region of the

first strand (pg. 21-22, Table 1). The reference also teaches that the amplification product can be isolated (pg. 24), and can then be resuspended to form a target solution. Smith also teaches that the ligase-mediated PCR technique can be used from polynucleotides derived from large molecules, such as YAC (pg. 25). In addition, Smith teaches that this method can be used in fingerprinting cosmids, YACS, and bacterial genomes or could be used for multiplex chromosome walking in clone libraries arrayed in high density grids (pg. 26). Smith does not teach using amplification products to generate an array.

Brown et al. teach methods for fabricating microarrays of biological samples. Smith teaches an apparatus for forming microarrays comprising; dispensing a known volume of a reagent at each selected array position, by tapping a capillary dispenser onto a support under conditions effective to draw a defined volume of liquid onto the support (abstract). The reference teaches that microarrays can be used in hybridizations assays, genetic and physical mapping of genomes, monitoring of gene expression, DNA sequencing, genetic diagnosis; genotyping of organisms, etc. (col. 14, ln. 35 to col. 15). The reference also teaches an example of using PCR amplified array elements in the microarray (col. 16-17). Furthermore, the reference teaches that the volume of each target applied to the substrate is 0.01 to 100 nanoliters (col. 3, ln. 39-41). The reference also teaches that the array comprises at least 1000 amplification products in a 1 cm^2 region of substrate (col. 4, ln. 16-19).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Smith so as to have applied the target solution comprising the amplified fragments to the microarray of Brown in order to have achieved the

benefits of producing an array useful for fingerprinting large molecules such as YACSs, cosmids, and bacterial genomes by DNA sequencing and gene expression analysis.

Applicants' traverse the obviousness rejection of Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), in view of Brown et al. (US 5,807,522, cited in the IDS). Applicants argue that Smith does not teach that the target solutions be "representative of the corresponding first polynucleotide". Applicants further argue that Brown does not teach or suggest any measures that would ensure that the product of amplification was representative of the corresponding starting polynucleotides. Applicants also argue that Brown does not teach the ligation of adaptors to polynucleotide fragments to produce modified polynucleotide fragments. Applicants also argue that Brown teaches the use of "random" PCR amplification, and that the products obtained using random primers are not generally representative of the starting nucleic acid.

Applicants arguments have been considered, but are not persuasive for the following reasons. First, it is noted that the teachings of Smith and Brown are to be used in combination with each other. As discussed above, Smith teaches that the target solutions be "representative of the corresponding first polynucleotide". Therefore, Smith is relied upon for teaching the production of a plurality of target solutions that are representative of the corresponding first polynucleotide (i.e. this includes the steps of providing a plurality of samples of double-stranded polynucleotide fragments and ligating adaptors to each end of said fragments). Brown is relied upon for a method and apparatus for applying target solutions to a substrate to fabricate microarrays. Applicants' arguments regarding Brown's alleged teaching of random PCR

amplification is moot, as Brown is not relied upon for teaching amplification. Therefore, in combination, the teachings of Smith and Brown teach all of the elements of the instant claims.

8. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), in view of Brown et al. (US 5,807,522, cited in the IDS), and in further view of Gordon et al. (US 5,601,980).

The teachings of Smith and Brown are presented above. The references do not teach the spotting of the target solutions on the substrate.

Gordon et al. teaches a manufacturing method and apparatus for biological probe arrays using vision-assisted micropipetting. Specifically, Gordon teaches a robotically manipulated micropipette which is used for spotting biological samples onto an array (col. 3, ln. 59-60).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Smith and Brown so as to have robotically spotted target solutions onto the substrate (i.e. array) in order to have achieved the benefits stated by Gordon of providing an accurate and cost effective spotting of miniscule volumes of biological material onto a substrate.

Applicants' traverse obviousness rejection of Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), in view of Brown et al. (US 5,807,522, cited in the IDS), and in further view of Gordon et al. (US 5,601,980). Applicants' argue that Gordon fails to provide the teaching of representative target solutions. This argument is not convincing as the teachings of Smith, Brown, and Gordon are to be used in combination with each other. As discussed above, Smith teaches that the target solutions be "representative of the corresponding first polynucleotide". Therefore, Smith is relied upon for teaching the production of a plurality of

target solutions that are representative of the corresponding first polynucleotide (i.e. this includes the steps of providing a plurality of samples of double-stranded polynucleotide fragments and ligating adaptors to each end of said fragments). Brown is relied upon for a method and apparatus for applying target solutions to a substrate to fabricate microarrays, and Gordon is relied upon for teaching the method of robotically spotting target solutions onto a substrate. Therefore, in combination, the teachings of Smith, Brown, and Gordon teach all of the elements of claim 17.

9. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), in view of Brown et al. (US 5,807,522, cited in the IDS), and further in view of Stimpson et al. (Proc. Natl. Acad. Sci. USA (1995) 92: 6379-6383).

The teachings of Smith and Brown are presented above. The references do not teach the method wherein at least one of the adapters includes an amino group.

Stimpson teaches the method of real-time detection of DNA hybridization and melting on oligonucleotide arrays by using optical wave guides. Specifically, Stimpson teaches DNA chips (i.e. array), which are constructed by using 3'-amino-labeled oligonucleotides (pg. 6380). Furthermore, Stimpson teaches that these amino-labeled oligonucleotides are immobilized onto the chip (6380).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Smith and Brown so as to have added an amino group to the adapter so as to have aided in the immobilization of the amplified polynucleotide onto the array.

Applicants' traverse obviousness rejection of Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), in view of Brown et al. (US 5,807,522, cited in the IDS), and in further view of Stimpson et al. (Proc. Natl. Acad. Sci. USA (1995) 92: 6379-6383): Applicants' argue that Stimpson fails to teach or suggest anything regarding an amplification-based method for producing target solutions representative of corresponding starting polynucleotides. This argument is not convincing as the teachings of Smith, Brown, and Stimpson are to be used in combination with each other. As discussed above, Smith teaches an amplification-based method for producing target solutions representative of corresponding starting polynucleotides. Therefore, Smith is relied upon for teaching the production of a plurality of target solutions that are representative of the corresponding first polynucleotide (i.e. this includes the steps of providing a plurality of samples of double-stranded polynucleotide fragments and ligating adaptors to each end of said fragments). Brown is relied upon for a method and apparatus for applying target solutions to a substrate to fabricate microarrays, and Stimpson is relied upon for providing an amino group to the adapter for binding to an array. Therefore, in combination, the teachings of Smith, Brown, and Stimpson teach all of the elements of claim 18.

10. Claims 19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), in view of Cronin et al. (WO 97/43450).

The teachings of Smith are presented above. The references do not teach resuspending the target solutions with dimethyl sulfoxide at a concentration of 20% by volume.

Cronin teaches hybridization assays on oligonucleotide arrays. Cronin teaches the method of performing a hybridization assay between a target nucleic acid molecule and an oligonucleotide array (comprising a plurality of discrete locations), wherein the array is incubated with a hybridization mixture comprising the target nucleic acid and a hybridization optimizing agent (pg. 17, ln. 1-8). The reference further teaches that the optimizing agent can be a denaturing agent (i.e. DMSO) (pg. 18, ln. 6-11). The reference teaches that denaturing agents lower the melting temperatures of double stranded nucleic acid molecules by interfering with hydrogen bonding between bases in a double stranded nucleic acid (pg. 5, ln. 31-33), therefore improving signal resolution in hybridization assays performed on substrate bound oligonucleotide arrays (pg. 2, ln. 14-17). The reference also teaches a range of concentrations of denaturing agents that can used for the hybridization mixture (pg. 6, ln. 1-2).

One of ordinary skill in the art would have been motivated to use the method of Smith to produce a target solution comprising dimethyl sulfoxide at a concentration of 20%, in order to provide a more effective hybridization assay to be performed on substrate bound oligonucleotide. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Smith of producing a target solution comprising dimethyl sulfoxide at a concentration of 20%, to provide a target solution suitable for application to an array of polynucleotides. While Cronin does not specifically teach a method using a concentration of 20% dimethyl sulfoxide, it is well known and common knowledge in the art that one of ordinary skill would use a solution of dimethyl sulfoxide at a concentration of 20% to optimize the hybridization reaction based on the concentration of the target nucleic acid and other reagents comprising the target solution.

Applicants' traverse obviousness rejection of Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), in view of Brown et al. (US 5,807,522, cited in the IDS), and in further view of Cronin et al. (WO 97/43450). Applicants' argue that Cronin fails to teach or suggest representative target solutions. This argument is not convincing as the teachings of Smith, Brown, and Cronin are to be used in combination with each other. As discussed above, Smith teaches an amplification-based method for producing target solutions representative of corresponding starting polynucleotides. Therefore, Smith is relied upon for teaching the production of a plurality of target solutions that are representative of the corresponding first polynucleotide (i.e. this includes the steps of providing a plurality of samples of double-stranded polynucleotide fragments and ligating adaptors to each end of said fragments). Brown is relied upon for a method and apparatus for applying target solutions to a substrate to fabricate microarrays, and Cronin is relied upon for the method of resuspending target solutions with dimethyl sulfoxide. Therefore, in combination, the teachings of Smith, Brown, and Cronin teach all of the elements of claims 19 and 22.

Conclusion

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
September 14, 2001

Kenneth R. Horlick, Ph. D.
KENNETH R. HORLICK
PRIMARY EXAMINER
GROUP 1600
9/19/01